Amendments to the Specification

Please amend paragraph [0012] of the published application as follows:

- - The minimal consensus sequence for efficient phosphorylation by PIM was found by Alessi et al. (Fed. Eur. Biochem Soc., 399, 333, 1996). This is a 7-mer motif faith the most active peptide substrate having the sequence Arg--Pro--Arg--Thr--Ser--Ser--Phe (SEQ ID NO: 1). International application WO 97122360 discloses certain PKB substrate peptides having 7-amino acids length, useful as substrate for measuring PKB activity. - -

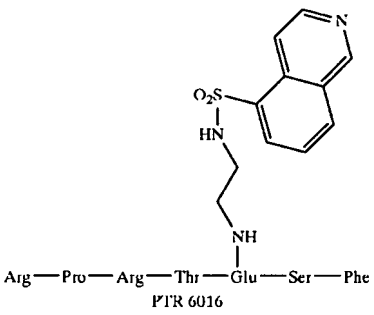
Please amend paragraph [0013] of the published application as follows:

- - Obata et al. (J. Biol. Chem., 17, 36108, 2000) described the use of an oriented peptide library approach to determine optimal amino acid sequence of the PKB substrate. All the substrates identified contained the known motif having the sequence Arg--Xaa--Arg--Xaa--[[Saa]]Xaa--Ser/Thr (SEQ ID NO: 2). - -

Please amend paragraph [0059] of the published application as follows:

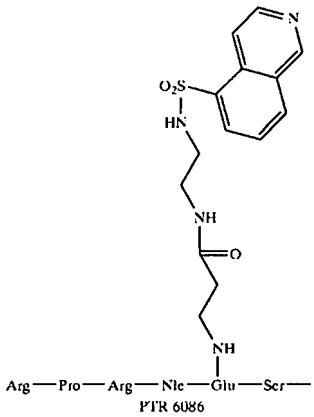
- - Currently most preferred embodiments of the present invention are the chimeric compounds of formulae III-VII:

Formula III



(SEQ ID NO: 12)

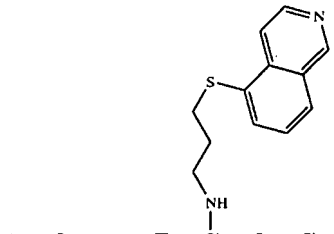
Formula IV



Arg—Pro—Arg—Nle—Glu—Ser—Phe (SEQ ID NO: 13)

PTR 6086

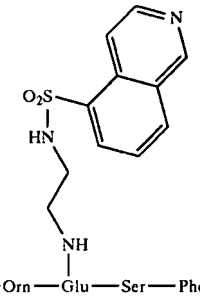
Formula V



Arg—Pro—Arg—Thr—Glu—Ser—Phe (SEQ ID NO: 14)

PTR 6104

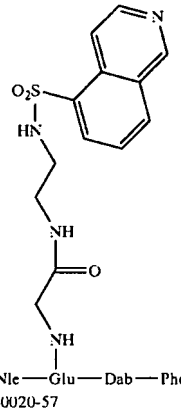
Formula VI



Arg—Pro—Arg—Orn—Glu—Ser—Phe (SEQ ID NO: 15)

PTR 6132

Formula VII



Arg—Pro—Arg—Nle—Glu—Dab—Phe (SEQ ID NO: 16) - -

PTR-60020-57

Please amend paragraph [0061] of the published application as follows:

- - Arg--Pro--Arg--Thr--Glu--(bAla-5-mercaptoaminopropyl-isoquinoline)--Ser--Phe (SEQ ID NO: 3). - -

Please amend paragraph [0062] of the published application as follows:

- - Arg--Pro--Arg--Thr--Glu--(5-mercaptoaminopropyl-isoquinoline)--Ser--Phe (SEQ ID NO: 4). - -

Please amend paragraph [0063] of the published application as follows:

- - Arg--Pro--Arg--Orn--Glu--(5-aminoethylsulfonamide isoquinoline)--Ser--Phe (SEQ ID NO: 5). - -

Please amend paragraph [0064] of the published application as follows:

- - Arg--Pro--Arg--Nva--Glu--(5-mercaptoaminopropyl-isoquinoline)--Ser--Phe (SEQ ID NO: 6). - -

Please amend paragraph [0065] of the published application as follows:

- - Arg--Pro--Arg--Nle--Glu--(5-mercaptoaminopropyl-isoquinoline)--Ser--Phe (SEQ ID NO: 7). - -

Please amend paragraph [0066] of the published application as follows:

- - Arg--Pro--Arg--Orn--Glu--(Gly-5-aminoethylsulfonamide)--Dab--Hol[[--]] (SEQ ID NO: 8). - -

Please amend paragraph [0067] of the published application as follows:

- - Arg--Pro--Arg--Nle--Glu--(Gly-5-aminoethylsulfonamide)--Dab--Phe (SEQ ID NO: 9). - -

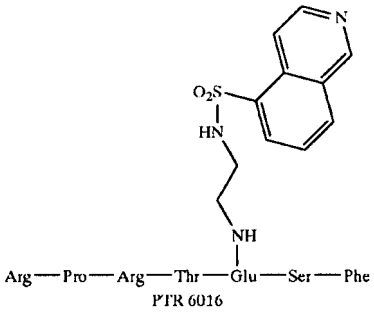
Please amend paragraph [0068] of the published application as follows:

- - Arg--Pro--Arg--Nle--Glu--(Gly-5-aminoethylsulfonamide)--Dab--Hol (SEQ ID NO: 10). - -

Please amend paragraph [0142] of the published application as follows:

- - Currently most preferred embodiments of the present invention include a chimeric compound selected from the compounds described hereinbelow in formulae III-VII:

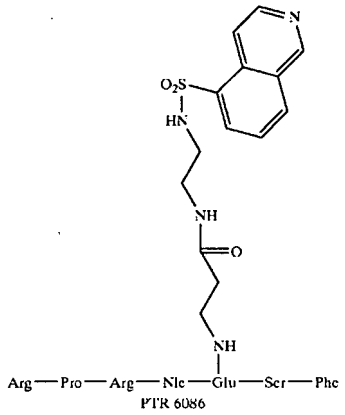
Formula III



(SEQ ID NO: 12)

PKB IC_{50}=900 nM PKA IC_{50}=100 nM

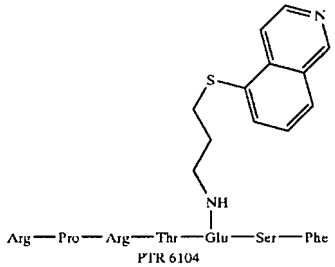
Formula IV



(SEQ ID NO: 13)

PKB IC_{50}=570 nM PKA IC_{50}=500 nM

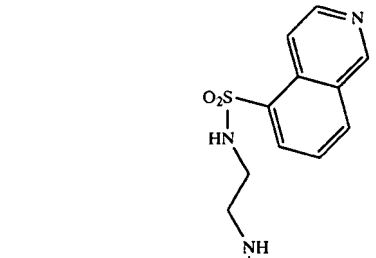
Formula V



(SEQ ID NO: 14)

PKB IC_{50}=100 nM PKA IC_{50}=100 nM

Formula VI

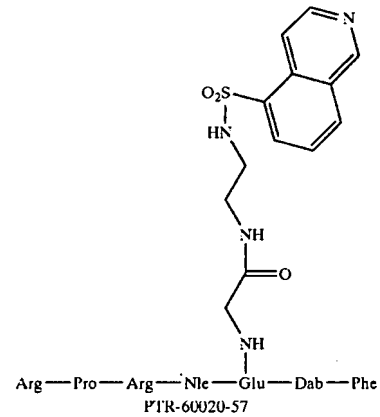


PTR 6132

(SEQ ID NO: 15)

PKB IC_{50}=20 nM PKA IC_{50}=12 nM

Formula VII



PTR-60020-57

(SEQ ID NO: 16) - -

PKB IC_{50}=70 nM PKA IC_{50}=210 nM - -

Please amend paragraph [0145] of the published application as follows:

- - Arg--Pro--Arg--Thr--Glu--(bAla-5-mercaptoaminopropyl-isoquinoline)--Ser--Phe (SEQ ID NO: 3). - -

Please amend paragraph [0146] of the published application as follows:

- - Arg--Pro--Arg--Thr--Glu--(5-mercaptoaminopropyl-isoquinoline)--Ser--Phe (SEQ ID NO: 4). - -

Please amend paragraph [0147] of the published application as follows:

- - Arg--Pro--Arg--Orn--Glu--(5-aminoethylsulfonamide-isoquinoline)--Ser--Phe (SEQ ID NO: 5). - -

Please amend paragraph [0148] of the published application as follows:

- - Arg--Pro--Arg--Nva--Glu--(5-mercaptoaminopropyl-isoquinoline)--Ser--Phe (SEQ ID NO: 6). - -

Please amend paragraph [0149] of the published application as follows:

- - Arg--Pro--Arg--Nle--Glu--(5-mercaptoaminopropyl-isoquinoline)--Ser--Phe (SEQ ID NO: 7). - -

Please amend paragraph [0150] of the published application as follows:

- - Arg--Pro--Arg--Orn--Glu--(Gly-5-aminoethylsulfonamide)--Dab--Hol[[--]] (SEQ ID NO: 8). - -

Please amend paragraph [0151] of the published application as follows:

- - Arg--Pro--Arg--Nle--Glu--(Gly-5-aminoethylsulfonamide)--Dab--Phe (SEQ ID NO: 9). - -

Please amend paragraph [0152] of the published application as follows:

- - Arg--Pro--Arg--Nle--Glu--(Gly-5-aminoethylsulfonamide)--Dab--Hol (SEQ ID NO: 10). - -

Please amend paragraph [0184] of the published application as follows:

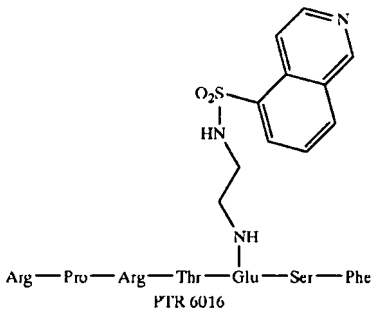
- - The inhibitor tested is dissolved in water to the desired concentration. Five μl of the inhibitor solution is added to the wells of a V shaped polyproplylene microplate. Five μl of substrate peptide (Biotin--Lys--Gly--Arg--Pro--Arg--Thr--Ser--Ser--Phe--Ala--Glu--Gly (SEQ ID NO: 11)) solution in water at a concentration of 300 μM is then added to the wells (final assay concentration is 100 μM). Then PKB enzyme dissolved in 3.times. reaction m (50 mM Tris HCl pH 7.5, 0.1% beta mercaptoethanol, 1 μM PKI (Calbiochem), 10 mM Mg acetate, ATP 5 μM), is added in pre-calibrated amount to the wells. The amount of enzyme is calibrated so that less than 10% of the substrate is phosphorylated by the end of the reaction as evaluated by mass spectral analysis. The plate is covered with an adhesive tape, placed over a 1 mm ID vortex

at 30.degree. C. and incubated for 30 min to 1 hour as needed. At the end of the incubation period 5 µl of 0.5 M disodium EDTA are added to the wells followed by 180 pd of PBS. - -

Please amend paragraph [0224] of the published application as follows:

- - Structures of PTR 6013, 6014 and 6020 are described in example 11. The structure of PTR 6016 is:

Formula III



PTR 6016

(SEQ ID NO: 12) - -

Please amend TABLE 3 of the published application as follows:

TABLE 3

ID	Structure	Activity PKB	Activity PKA
TY 60002-50:	Arg-Pro-Arg-Thr-Ser-Ala-Hol (SEQ ID NO: 17)	5 µM	>40 µM
TY 60002-61:	Arg-Pro-Arg-Val-Ser-Abu-Phe (SEQ ID NO: 18)	5 µM	>40 µM
TY 60002-73:	Arg-Pro-Arg-Thr-Ser-Abu-Hol (SEQ ID NO: 19)	5 µM	>40 µM
TY 60002-96:	Arg-Pro-Arg-Thr-Ser-Dap-Hol (SEQ ID NO: 20)	5 µM	>40 µM
TY 60002-18:	Arg-Pro-Arg-Thr-Ser-Asp-Phe (SEQ ID NO: 21)	Not active	
AR 60003-50:	Arg-Pro-Arg-Met-Ser-Ser-Phe (SEQ ID NO: 22)	2.5 µM	
AR 60003-52:	Arg-Pro-Arg-Orn-Ser-Ser-Phe (SEQ ID NO: 23)	2.5 µM	
AR 60003-53:	Arg-Pro-Arg-Arg-Ser-Ser-Phe (SEQ ID NO: 24)	3 µM	
AR 60003-62:	Arg-Pro-Arg-Nle-Ser-Ser-Nle (SEQ ID NO: 25)	<1 µM (70% inhibition at 1 µM)	
AR 60003-64:	Arg-Pro-Arg-Arg-Ser-Ser-Arg (SEQ ID NO: 26)	Not active	
AR 60003-64:	Arg-Pro-Arg-Orn-Ala-Thr-Orn (SEQ ID NO: 27)	Not active	

The PKB inhibition activity of peptide AR-60003-52 as determined in ELISA is illustrated in FIG. 2.

Please amend TABLE 8 of the published application as follows:

TABLE 8

PTR	Structure	PKB IC_{50} (μM)	PKA IC_{50} (μM)
6013:	Arg-Pro-Arg-Thr-Ser-Abu-Phe-(O-CO-N-SO2-IQ) (SEQ ID NO: 28)	4	na
6014:	Arg-Pro-Arg-Thr-Ser-Glu-(CO-N-SO2-IQ)-Phe (SEQ ID NO: 29)	25	na
6016:	Arg-Pro-Arg-Thr-Glu-(CO-N-SO2-IQ)-Ser-Phe (SEQ ID NO: 12)	1	0.1
6020:	Arg-Pro-Arg-Thr-Ser-Abu-Phe-(O-CO-N-bAla-SO2-IQ) (SEQ ID NO: 30)	18	na
6082:	Arg-Pro-Arg-Thr-Glu-(CO-N-bAla-SO2-IQ)-Ser-Phe (SEQ ID NO: 31)	5.54	0.2
6086:	Arg-Pro-Arg-Nle-Glu-(CO-N-bAla-SO2-IQ)-Ser-Phe (SEQ ID NO: 13)	0.57	0.5
6088:	Arg-Pro-Arg-Orn-Glu-(CO-N-bGaba-SO2-IQ)-Ser-Phe (SEQ ID NO: 32)	1.18	1
6090:	Arg-Pro-Arg-Thr-Glu-(CO-N-Ape5-SO2-IQ)-Ser-Phe (SEQ ID NO: 33)	5.6	0.6
6096:	Arg-Pro-Arg-Nle-Glu-(CO-N-bAla-SO2-IQ)-Ser-Nle (SEQ ID NO: 34)	0.93	0.2
6102:	Arg-Pro-Arg-Thr-Glu-(CO-N-bAla-S-IQ)-Ser-Phe (SEQ ID NO: 35)	0.3	0.1
6104:	Arg-Pro-Arg-Thr-Glu-(CO-N-S-IQ)-Ser-Phe (SEQ ID NO: 14)	0.1	0.1
6106:	Arg-Pro-Arg-Thr-Dap-(N-CO-SO2-IQ)-Ser-Phe# (SEQ ID NO: 36)	10	na
6128:	Arg-Pro-Arg-Nle-Glu-(CO-N-SO2-IQ)-Ser-Phe (SEQ ID NO: 37)	9	0.1
6130:	Arg-Pro-Arg-Thr-Asp-(CO-N-SO2-IQ)-Ser-Phe (SEQ ID NO: 38)	9.5	0.053
6132:	Arg-Pro-Arg-Orn-Glu-(CO-N-SO2-IQ)-Ser-Phe (SEQ ID NO: 15)	0.02	0.012
6134:	Arg-Pro-Arg-Nva-Glu-(CO-N-S-IQ)-Ser-Phe (SEQ ID NO: 39)	0.217	0.018
6136:	Arg-Pro-Arg-Nle-Glu-(CO-N-S-IQ)-Ser-Phe (SEQ ID NO: 40)	0.114	0.011
6138:	Arg-Pro-Arg-Nle-Glu-(CO-N-bAla-SO2-IQ)-Abu-Phe (SEQ ID NO: 41)	2	na
6140:	Arg-Pro-Arg-Nle-Glu-(CO-N-bAla-SO2-IQ)-Dab-Phe (SEQ ID NO: 42)	0.413	0.195
6150:	Arg-Pro-Arg-Nva-Glu-(CO-N-SO2-IQ)-Ala-Hol (SEQ ID NO: 43)	25	na
6152:	Arg-Pro-Arg-Nva-Glu-(CO-N-bAla-SO2-IQ)-Ala-Hol (SEQ ID NO: 44)	5	5

# the small molecule of this compound is connected to the peptide via an amide bond between an amine of Dap residue on the peptide and the carboxylic acid on the small molecule, while in the other compounds the small molecule is connected to the peptide via an amide bond between a carboxylic moiety on the peptide and amino moiety on the small molecule.
na = not assayed
SO2-IQ = 5-aminoethylsulfoneamide isoquinoline
S-IQ = 5-mercaptoaminopropyl isoquinoline